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EXAMINER	
FOSTER, CHRISTINE E	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/811,130	DEVARAJAN ET AL.	
	Examiner	Art Unit	
	Christine Foster	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *3/4/09*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,4,5,9-11,33,35,37,55,60 and 66* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,4,5,9-11,33,35,37,55,60 and 66* is/are rejected.

7)☒ Claim(s) *55* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *3/26/2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Amendment Entry

1. Applicant's amendment, filed 3/4/2009, is acknowledged and has been entered. Claims 2, 4-5, 9, 33, 35, 37, 55, and 60 were amended. Claims 1, 30-31, 48, 52, and 61-65 were canceled. New claim 66 has been added. Accordingly, claims 2, 4-5, 9-11, 33, 35, 37, 55, 60, and 66 are currently pending and subject to examination below.

Objections/ Rejections Withdrawn

2. The objection to the specification has been obviated by Applicant's amendments thereto.

3. The objections to claims 1 and 30 are moot in light of Applicant's cancellation of these claims.

4. The rejections of claims 1, 30-31, 48, 52, and 61-65 have been withdrawn in response to Applicant's cancellation of these claims.

5. The rejections under § 112, 1st paragraph have been withdrawn in response to Applicant's amendments and in view of the cancellation of the above-mentioned claims.

6. The provisional obviousness-type double patenting rejections over copending Application No. 11/770,214 have been withdrawn in view of the abandonment of the copending application.

Priority

7. The present application was filed on 3/26/2004. Acknowledgment is made of applicant's claim under 35 U.S.C. 119(e) for benefit of the earlier filing dates of provisional application No.

60/458,143 (filed on 03/27/2003) and of provisional application No. 60/481,596, (filed 11/04/2003).

8. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed applications, Application Nos. 60/458,143 and 60/481,596, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application.

Specifically, support for the subject matter of **claims 37 and 60** could not be found in the provisional applications.

Claim 37 recites that the renal tubular cell injury is caused by an event which may be "open heart surgery" or "cardiac surgery". Similarly, claim 60 recites that the method is performed on a patient who has undergone "open heart surgery".

Application No. 60/458,143 discloses methods in which renal tubular cell injury may be caused by an event, including "surgical procedures", "cardiovascular events", "vascular

surgery", or "kidney transplants". See page 3, line 10; page 5, lines 22-26; and page 11 in particular. However, "open heart surgery" and "cardiac surgery" are not disclosed. Although these may be considered to be species reading on the genera of "surgical procedures" or "cardiovascular events", there is insufficient direction to the species given the large number of species that would be encompassed, as well as the variability within these genera.

Similarly, Application No. 60/481,596 discloses that renal tubular cell injury may be caused by an event (claim 19), including "surgical procedures" (claim 32) or impaired heart function (page 14). However, "open heart surgery" and "cardiac surgery" are not disclosed. One skilled in the art cannot envisage these specific events based on the general disclosure in the provisional application, given the large number of various events that would be encompassed by "surgical procedures", for example.

For these reasons, the priority date of claims 37 and 60 is 3/29/04. New claim 66 has an effective filing date of 3/27/2003. Claims 2, 4-5, 9-11, 33, 35, and 55 as amended now have an effective filing date of 3/27/2003, as a result of Applicant's amendments such that these claims now depend from new claim 66.

Claim Objections

9. Claim 55 is objected to because of the following informalities:

10. Claim 55 refers to "the acute ischemic renal tubular cell injury". However, independent claim 66 does not recite an "acute" ischemic renal tubular cell injury, such that the dependent claim may present confusion. It is suggested that claim 55 refer to "the renal tubular cell injury"

or to "the ischemic renal tubular cell injury" in accordance with language used in the independent claim.

Claim Rejections - 35 USC § 112

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claim 60 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

13. Claim 60 recites "a urine sample obtained at 2 hours" but does not specify what this time point is in relation to. Absent a frame of reference for understanding what the initial or zero time point with respect to which the sample is being later obtained, the scope of the claim is unclear. For the purposes of examination, the claim was interpreted as meaning that the urine sample is obtained 2 hours after open heart surgery.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

16. Claims 4-5, 9-11, 33, 35, 37, 55, and 66 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Matthaeus et al. ("Acute Ischemic Renal Failure Induces Expression of Neutrophil Gelatinase-Associated Lipocalin and Matrix Metalloproteinase-9 in Damaged Tubuli" *Kidney Blood Press Res* (2001), Vol. 24, page 342, abstract No. P268; hereafter, "Matthaeus 1") or Matthaeus et al. ("Co-Regulation of Neutrophil Gelatinase-Associated Lipocalin and Matrix Metalloproteinase-9 in the Postischemic Rat Kidney" *J. Am Soc Nephrol* Vol. 12, September 2001, Pathophysiology of Renal Disease, pp. 787A; A4112, SUI-0348 (PS), Applicant's IDS of 11/13/07; hereafter, "Matthaeus 2" in view of Ramsden et al. (US 4,640,909), Blaser et al. ("A sandwich enzyme immunoassay for the determination of neutrophil lipocalin in body fluids" Clin Chim Acta. 1995 Mar 31;235(2):137-45, Applicant's IDS of 7/24/06), Moses et al. (US 7,153,660 B2), David et al. (US 4,376,110), and Muramatsu (Kidney International, Vol. 62 (2002), pages 1601-1610, Applicant's IDS of 10/18/04; or, in the alternative, over either Matthaeus 1 or Matthaeus 2 and Ohlsson et al. ("Increased circulating levels of proteinase 3 in patients with anti-neutrophilic cytoplasmic autoantibodies-associated systemic vasculitis in remission" Clin Exp Immunol. (available online February 28, 2003) 131(3):528-35, see Applicant's IDS of 7/24/06) in view of Ramsden et al., Blaser et al., Moses et al., David et al.,

and Muramatsu (Kidney International, Vol. 62 (2002), pages 1601-1610, Applicant's IDS of 10/18/04).

Matthaeus 1 teach that levels of NGAL protein are upregulated in response to experimentally induced acute ischemic renal injury in a rat model (i.e., ischemic renal tubular cell injury; see entire selection). By contrast, control animals displayed only minor expression of NGAL, demonstrating that renal injury and repair is associated with an upregulation of NGAL (i.e., correlating the level of NGAL with ischemic renal tubular cell injury). Matthaeus 1 further report that NGAL was elevated "after 24 and 48 hours" of renal ischemia as assessed by Western blot analysis.

Similarly, Matthaeus 2 teaches that NGAL protein expression was upregulated after ischemic injury in a rat model of renal ischemia, demonstrating that upregulation of NGAL is associated with renal injury as well as repair (see entire selection). The reference further teaches that NGAL may play a critical role in the renal response to ischemic injury (last sentence).

The Matthaeus references differ from the claimed invention in that they fail to specifically teach detecting NGAL in **urine** as claimed; rather, the references detected NGAL in the postischemic kidney (tissue). Furthermore, the references fail to teach detecting NGAL in urine samples taken "*within four hours of the RTCI*". Finally, Matthaeus 1 and Matthaeus 2 detected NGAL protein expression via Western blot analysis, but are silent as to whether their procedures involved formation and detection of an antibody- NGAL complex.

With respect to the limitation that NGAL is detected in urine, is noted that the Matthaeus references make clear that their studies were performed on rats *as an animal model of human disease* (this is made explicit in Matthaeus 2, who refer to a "rat model of renal ischemia"). ,

Matthaeus 1 state that the purpose of their experiment is to "further elucidate the processes involved in renal injury and repair". The findings reported therein support a "critical role in the renal response to injury" for NGAL, correlating upregulation of NGAL with ischemic renal tubular cell injury.

It was well known in the art that disease processes may produce changes in the levels of certain specific analytes, and that measurement of the levels of such analytes can be used to detect the presence of the disease. This is taken to be admitted prior art because applicant has failed to traverse this assertion (see MPEP 2144.03).

Therefore, it would have been obvious to one of ordinary skill in the art detect NGAL for the purpose of diagnosing acute renal injury in light of the teachings of Matthaeus 1 or Matthaeus 2 that NGAL is specifically elevated in this disease condition, and further in view of the general knowledge of one skilled in the art that markers changed in response to disease can be used as biomarkers for diagnosis of the disease.

Put another way, it would have been obvious to one of ordinary skill in the art at the time of the instant invention to conclude from the findings of Matthaeus 1 or 2 that NGAL could be used as a biomarker of renal ischemia, such that it would have been obvious to detect NGAL in human subjects for the clear benefit of diagnosing human disease.

In such a case, it would have been further obvious to employ urine as the sample source, rather than the kidney tissue samples examined in the rat models of Matthaeus 1 and 2, for the following reasons.

Initially, it is noted that one skilled in the art would immediately recognize that isolation of kidney tissue would be very invasive and therefore unsuitable method for diagnosing renal injury in humans.

Alternative sources of samples for biomarker detection were known in the art. Specifically, it was well known to one skilled in the art of biochemical assay at the time of the invention that urine is a non-invasive and easily collected type of sample. See for example Ramsden et al., column 1, lines 15-16, which teaches that urine samples are noninvasive and convenient.

Therefore, in light of the general knowledge of one skilled in the art that urine is an easily collected and non-invasive sample source for assay of biological analytes (as taught for example by Ramsden et al.), it would have been obvious to use urine as the sample source instead of kidney tissue samples when detecting NGAL for diagnosis of ischemic renal injury in human subjects, for the advantage of being a non-invasive and easily collected sample.

One would have a reasonable expectation of success because it was known in the prior art that NGAL is excreted in urine, as taught by Blaser et al. and Moses et al.

In particular, Blaser et al. teach detection of human neutrophil lipocalin (NGAL) in urine by sandwich ELISA (see in particular the abstract; page 139, section 2.4; and pages 142-143, sections 3.3-3.4). Moses et al. also teach that NGAL may be detected in human urine by Western Blot (Example 2 and Figure 1B).

As such, in light of the teachings of Blaser et al. and Moses et al., one skilled in the art would have a reasonable expectation of success in using urine as a sample source for detection of

NGAL in response to renal injury (rather than kidney tissue as taught by Matthaeus 1 and 2) since NGAL was known at the time of the instant invention to be excreted in urine.

With respect to the combination of the Matthaeus 1 or 2, Ohlsson et al., Ramsden et al., Blaser et al., and Moses et al. references, it is noted that Ohlsson et al. adds additional evidence that NGAL was known to be elevated in the context of renal injury at the time of the instant invention.

Specifically, Ohlsson et al. teach an ELISA method to detect NGAL in human blood plasma samples (p. 530, left column; p. 531, the section "PR3 versus neutrophil activation and degranulation"; Figures 3-4; and Table 4b in particular). In particular, Ohlsson et al. specifically looked at patients with ANCA-associated systemic vasculitis and recorded development of renal failure (p. 529 "Patient material"). Ohlsson et al. found that ***greatly elevated NGAL levels are strongly correlated with decreased renal function*** (p. 531, the left column, last paragraph).

Taken together with the findings of Matthaeus 1 or 2, it would have been obvious to detect NGAL for the purpose of diagnosing renal dysfunction since the references establish that NGAL is specifically elevated in this disease condition, and further in view of the general knowledge of one skilled in the art at the time of the invention that markers changed in response to disease can be used as biomarkers for diagnosis of the disease.

As above, although Matthaeus 1, Matthaeus 2, and Ohlsson et al. did not examine NGAL levels in urine (Ohlsson et al. employed blood plasma), it would have been obvious to use urine as the sample source instead of the kidney tissue samples when detecting NGAL for diagnosis of

renal injury in human subjects, for the advantage of being a non-invasive and easily collected sample (as taught by Ramsden et al.).

One would have a reasonable expectation of success because it was known in the prior art that NGAL is excreted in urine, as taught by Blaser et al. and Moses et al.

With respect to the limitation that detection involves an antibody for NGAL and detection of the resulting antibody-NGAL complex, David et al. teach sandwich or "two-site" immunoassays for detecting the presence of analytes in fluids, in which an unlabeled "capture" antibody is bound to a media (solid support) and then contacted with a sample containing the analyte (see in particular the abstract; column 3, line 10 to column 6, line 61, and especially column 4, lines 19-37). After formation of a capture antibody-analyte complex, a second labeled antibody is added which recognizes a different site on the analyte, resulting in the formation of a "sandwich" (see especially column 1, line 47 to column 2, lines 17; column 5, lines 45-60). This type of assay format has great utility in detecting the presence or amount of an analyte, and the improvements reported by David et al. also produce an assay format that is rapid and sensitive while eliminating false positive results (column 8, lines 33-38; and also column 1, line 67 to column 2, line 7).

Therefore, it would have obvious to one of ordinary skill in the art to detect NGAL in the prior art methods as discussed above using the well known sandwich immunoassay format, as taught for example by David et al. One would be motivated to employ this method to detect the presence of NGAL because it is well recognized in the prior art to be a rapid and sensitive method of detecting analytes in a fluid sample.

With respect to claims 10-11, the method of David et al. involves contacting the fluid sample with the media (solid phase) upon which the primary antibody has been immobilized (see for example column 1, lines 47-56; column 6, lines 5-17; and the Example).

With respect to the limitation that NGAL is detected urine samples taken "*within four hours of the RTCI*", it is noted that Matthaeus 1 and Matthaeus 2 each teach that NGAL was elevated in kidney (tissue) "after 24 and 48 hours" of renal injury (ischemia induced by operation). Matthaeus 1 also clearly teaches NGAL upregulation in the context of *acute* ischemic renal failure (title). However, the references do not discuss whether samples were also taken at other, earlier time points.

Muramatsu et al. teach that it is imperative to diagnose acute renal failure (ARF) as soon as possible, and that disease markers that can be measured in blood or urine would be of extreme value since ARF is associated with high morbidity and mortality (see especially page 1601).

In particular, the reference teaches screening for a biomarker of ARF (Cyr61) by detecting the presence of urinary Cyr61 within specified times in relation to the onset of induced renal ischemia, as a model of ARF (see especially pages 1603-1604, "Urine Collection"; page 1606; and Figure 8). The reference exemplifies time points of 3-6, 6-9, 9-12, 12-18, and 18-24 hours after ischemia (see especially the legend to Figure 8) and report that the levels of urinary Cyr61 were seen to increase within 3-6 hours (page 1608). The reference also teaches that no urine was produced within the first three hours, such that the first time point of 3-6 hours would represent the first urine output (legend to Figure 8).

Therefore, it would have been further obvious to one of ordinary skill in the art to detect NGAL levels as early as possible as taught by Muramatsu, and in particular within the recited time ranges in relation to the onset of injury out of the normal desire of artisans to improve upon what is already known. See MPEP 2144.05. In particular, one would be motivated to detect NGAL within 24 hours or earlier in order to diagnose disease earlier, and therefore to allow for timely interventions to be performed. Given that Muramatsu exemplifies 3-6 hours, thereby teaching a range that overlaps the claimed range of "within four hours", it would have been obvious to arrive at the claimed invention out of the course of routine optimization by selecting any point within the prior art range. Further, one would be motivated to detect NGAL within four hours in order to diagnose disease earlier, and therefore to allow for timely interventions to be performed.

One would have a reasonable expectation of success because the teachings of Muramatsu et al. indicate that biomarkers of ARF were known to be detectable in urine within 3-6 hours.

With respect to claim 37, Muramatsu et al. further teach that the biomarker Cyr61 is rapidly induced in the kidney in response to renal ischemia, and that because of this rapid induction pattern, it may serve as an early disease marker for renal injury (see the paragraph bridging pages 1608-1609). The reference further indicates that the marker could be used in a variety of settings including after contrast administration, chemotherapy, transplantation, vascular surgery, or in kidney donors, or with multi-organ failure in the ICU.

One skilled in the art would clearly appreciate the parallels between the biomarker Cyr61 as taught by Muramatsu and the NGAL protein taught by Matthaeus 1 (and also by Ohlsson et

al.). Matthaeus 1 teach that like Cyr61, NGAL is upregulated in response to renal ischemia. Taken together with the teachings of Muramatsu et al. that a marker exhibiting this property may serve as an early disease marker for renal injury after transplantation or vascular surgery, one skilled in the art would be highly motivated to employ NGAL as a biomarker of renal tubular cell injury for this same purpose. For example, it would have been obvious to detect NGAL in the context of transplantation or vascular surgery for the purpose of diagnosing ARF.

With respect to claim 5, as noted above, one would be motivated to detect NGAL in humans for the purpose of diagnosing human disease. One would have a reasonable expectation of success because Matthaeus 1 and 2 clearly indicate that detection of NGAL in rats was done as an animal model, i.e. an animal model of human disease, and further because Ohlsson et al., Moses et al. and Blaser et al. each teach that NGAL is also expressed in humans. The Ohlsson et al. reference also establishes that NGAL levels in humans are correlated with renal dysfunction.

With respect to claim 33, Muramatsu exemplifies examining Cyr61 as a renal ischemic injury biomarker at time points of 3-6, 6-9, 9-12, 12-18, and 18-24 hours after ischemia (see especially the legend to Figure 8) and report that the levels of urinary Cyr61 were seen to increase within 3-6 hours (page 1608). The reference also teaches that no urine was produced within the first three hours, such that the first time point of 3-6 hours would represent the first urine output (legend to Figure 8). When taken together with the general knowledge in the art regarding the urgency of detecting ARF as early as possible, it would also have been obvious to detect urinary NGAL as a biomarker of ARF as early as possible in this same manner.

With respect to claim 55, which recites that the level of antibody-NGAL complex correlates with the extent of injury, it is noted that while the claim might suggest additional steps,

none are recited or clearly required by the claim. Claim scope is not limited by such language (see MPEP 2111.04). Accordingly, the reference teachings read on the claim since this statement may be interpreted (for example) as simply describing properties of NGAL and does not require additional steps or elements. In other words, when performing the prior art methods as discussed above, it would necessarily follow that the level of detected antibody-NGAL complex would correlate with the extent of the ischemic renal tubular cell injury.

17. Claims 4-5, 9-11, 33, 35, 55, and 66 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Matthaeus 1 or Matthaeus 2 in view of Ramsden et al., Blaser et al., Moses et al., David et al., and Sanicola-Nadel et al. (U.S. 6,664,385).

New claim 66, and amended claims 2, 4-5, 9-11, 33, 35, and 55 (which now depend from new claim 66) have an effective filing date of 3/27/2003. Upon reevaluating the claims in light of the earlier effective filing date, the following rejection is being made in accordance with MPEP 904.03 and 706.02 (I).

The teachings of Matthaeus 1, Matthaeus 2, Ramsden et al., Blaser et al., Moses et al., and David et al. are discussed in detail above, which teach a method for detecting an ischemic renal tubular cell injury by detecting NGAL in urine substantially as claimed. Please refer to the detailed analysis above.

The references differ from the claimed invention in that they fail to specifically teach detecting NGAL in a urine sample obtained "*within four hours of the RTCI*". Matthaeus 1 and Matthaeus 2 each teach that NGAL was elevated in kidney (tissue) "after 24 and 48 hours" of renal injury (ischemia induced by operation).

Sanicola-Nadel et al. teach Kidney Injury-related Molecules or "KIMs", which are molecules that are upregulated in renal tissue after injury to the kidney (e.g., ischemic injury). See column 5, lines 16-27. The reference teaches that such KIM proteins can be used in diagnostic methods (such as assessing the presence or course of resolution of renal injury) by measuring the concentration of the proteins in urine, serum, or kidney tissue. See the abstract; column 1, lines 49-55; column 2, line 66 to column 3, line 21; and column 17, lines 34-41. *The presence or abnormal elevation of KIM protein in urine or serum is expected to correlate with renal failure or renal disease* (column 3, line 14-16). Sanicola-Nadel et al. also teach the use of antibodies to detect proteins (column 16, lines 50-67; column 17, lines 34-42).

Sanicola-Nadel et al. further teach that proteins that are selectively upregulated following injury to a kidney can be identified at any time within one week following any insult that results in injury to renal tissue. Examples of times at which such upregulation might be identified include 10 hours, 24 hours, 48 hours or 96 hours following an insult. See column 5, lines 17-27. It is noted that the claimed range of a sample obtained "within four hours of the RTCI" lies inside the prior art range of detection "within one week" disclosed by Sanicola-Nadel et al.

When taken together with the teachings of Matthaeus 1 or Matthaeus 2, Ramsden et al., Blaser et al., Moses et al., David et al., therefore, it would have been *prima facie* obvious to arrive at the claimed range of "within four hours" by selecting any time period within the prior art range of "within one week" as taught by Sanicola-Nadel et al. See MPEP 2144.05 (I). Furthermore, when taken together with the general knowledge in the art regarding the urgency of detecting ARF as early as possible, it would also have been obvious to detect urinary NGAL as a biomarker of ARF as early as possible in this same manner.

18. Claim 2 is rejected under 35 U.S.C. 103(a) as being unpatentable over Matthaeus 1 or 2 in view of Ramsden et al., Blaser et al., Moses et al., David et al. and Muramatsu et al.; or in the alternative over Matthaeus 1 or 2 and Ohlsson et al. in view of Ramsden et al., Blaser et al., Moses et al., David et al. and Muramatsu et al.; or in the alternative over Matthaeus 1 or Matthaeus 2 in view of Ramsden et al., Blaser et al., Moses et al., David et al., and Sanicola-Nadel et al.; all as applied to claim 66 above, and further in view of either one of Valkirs et al. (US 2003/0109420 A1) or Linzer et al. (US 3,635,091).

The references are as discussed above, which teach a method for detecting NGAL in a urine sample substantially as claimed, but which fail to specifically teach that the urine sample comprises a plurality of urine samples that are obtained "intermittently or continuously".

Valkirs et al. teach that one skilled in the art would recognize the value of testing multiple samples (for example, a series of samples obtained at successive time points) from the same individual, e.g. in allowing identification of changes in levels of markers over time [0107]. Such data can provide information about disease status, including appropriateness about drug therapies and identification of patient outcome.

Therefore, it would have been obvious to one of ordinary skill in the art to collect a plurality of urine samples at successive time points, i.e. intermittently as taught by Valkirs et al. in order to obtain information about renal disease status over time.

Linzer et al. teach a urine sample collector in which urine obtained by having the patient urinate continuously into the container (see especially column 1, lines 1-45 and column 2, lines 46-57). The collector separates the urine into two fractions, so that if necessary the initial urine

fraction can be compared with the midstream specimen (column 2, lines 46-57). The collector can also be adapted so that the liquid can be deposited into multiple independent containers (the abstract). The reference teaches that the sample collector has the advantage in that it provides a specimen free of contamination (column 1, lines 1-73).

Therefore, it would also have been obvious to obtain multiple urine samples in a continuous fashion (continuous stream of urine) using the urine specimen collector of Linzer et al. in order to ensure that the analyzed sample was free of contamination.

19. Claim 55 is also rejected under 35 U.S.C. 103(a) as being unpatentable over Matthaeus 1 or Matthaeus 2 in view of Ramsden et al., Blaser et al., Moses et al., David et al., and Muramatsu et al.; or, in the alternative, over Matthaeus 1 or Matthaeus 2 and Ohlsson et al. in view of Ramsden et al., Blaser et al., Moses et al., David et al., and Muramatsu et al.; or, in the alternative, over Matthaeus 1 or Matthaeus 2 in view of Ramsden et al., Blaser et al., Moses et al., David et al., and Sanicola-Nadel et al., all as applied to claim 66 above, and further in view of Kosako et al. (US 5,527,714).

The references discussed in detail above. As also discussed above, the claim at issue may suggest but does not clearly require correlation with the extent of injury. Even if the claim is interpreted as requiring an active method in which the level of antibody-NGAL complex is correlated to the extent of the acute renal tubular cell injury, the claim is nonetheless found obvious for the following reasons.

Kosako et al. teaches antigen/antibody reactions to prepare an analyte for diagnosis, in which the level of antigen/antibody complex as measured using a detectable marker is measured.

The amount of marker that is bound to the analyte (antigen) directly correlates with the amount of analyte in the sample and *becomes an index of the presence or extent of a disease* (column 1, lines 18-28).

The teachings of Kosako et al. establish that it was known to use markers of disease not only to indicate the presence of a disease but also its extent or severity.

Therefore, when taken together with the teachings of Matthaeus 1 or Matthaeus 2 in particular which establish NGAL as a marker of acute ischemic renal injury, it would have been further obvious to one of ordinary skill in the art to correlate NGAL levels not only with the presence of disease but also with the extent or severity of disease.

20. Claim 60 is rejected under 35 U.S.C. 103(a) as being unpatentable over Matthaeus 1 in view of Ramsden et al., Blaser et al., Moses et al., David et al., and Muramatsu et al.; or, in the alternative, over Matthaeus 1 and Ohlsson et al. in view of Ramsden et al., Blaser et al., Moses et al., David et al., and Muramatsu et al.; or, in the alternative, over Matthaeus 1 in view of Ramsden et al., Blaser et al., Moses et al., David et al., and Sanicola-Nadel et al., all as applied to claim 66 above, and further in view of Zanardo et al. ("Acute renal failure in the patient undergoing cardiac operation. Prevalence, mortality rate, and main risk factors" J Thorac Cardiovasc Surg. 1994 Jun;107(6):1489-95).

The prior art references discussed in detail above fail to specifically teach detecting a renal tubular cell injury (RTCI) in patients who have undergone open heart surgery, or that at least a 10-fold increase in the level of antibody-NGAL complex in urine samples obtained at 2 hours in such patients correlates with the RTCI progressing to ARF.

Zanardo et al. teach that patients undergoing major surgical procedures, and in particular cardiovascular bypass surgery (i.e., open heart surgery), are at risk for the development of acute renal (see the title, abstract, and page 1489). The authors assessed renal injury using serum creatinine as a marker, which was measured before, during, and after the operation. See page 1490, "Methods" and page 1492, Table II. This was done so that postoperative renal function could be assessed in terms of preoperative, intraoperative and postoperative clinical variables. In particular, Zanardo et al. discuss how patients undergoing major surgical procedures are at risk of postoperative acute renal failure (page 1489).

Based on the teachings of Zanardo et al. that patients who undergo open heart surgery are at risk for developing acute renal failure, it would have been obvious to one of ordinary skill in the art to select such patients when performing the prior art methods of detecting acute ischemic renal failure as discussed in detail above. One would be motivated to do this because such patients were known to be at risk of acute renal failure. As such, when taken together with the general knowledge in the art, it would have been obvious to combine the reference teachings in this manner so as to screen those individuals at risk for the presence of disease.

With respect to the recitation that the sample is obtained at 2 hours, which is presumed to refer to 2 hours after open heart surgery (see rejection under § 112, 2nd paragraph above), Zanardo et al. measured serum creatinine as a marker of renal function at the time of weaning from CBP (see Table II). As listed in the Table, bypass time was approximately 2-3 hours (see "CBP time (min)").

It would have been obvious to detect NGAL in patients undergoing CBP at the time of CPB weaning in this same manner, in order to assess renal function. Because bypass time is

disclosed by Zanardo et al. to last approximately 2-3 hours, it would have been obvious to arrive at the claimed invention depending on the particular bypass time for the patient under study.

With respect to the recitation that the level of antibody-NGAL complex in the sample correlates with the RTCI progressing to ARF, Matthaeus 1 teaches that NGAL is upregulated in the context of acute renal failure induced by ischemic injury (see entire selection, including title). Consequently, when detecting NGAL as an indicator of renal function in CBP patients according to the prior art methods as discussed above, it would be to be expected and would also necessarily follow that antibody-NGAL complex levels would correlate with the progression to ARF in these patients.

Double Patenting

21. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

22. Claims 2, 4-5, 9-11, 33, 35, 37, 55, 60, and 66 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 2, 4, 7-10, and 22-39 of copending Application No. 11/096,113 in view of Ramsden et al., Blaser et al., and Moses et al.

Copending application No. 11/096,113 recites a method identifying if a mammalian subject has an acute renal tubular cell injury in a mammalian subject based on the level of NGAL in a sample (see especially claims 22, 27, and 31). The renal tubular cell injury may be ischemic (see claim 34). The level of NGAL may be determined by contacting a sample with an antibody for NGAL and detecting the resulting antibody-NGAL complex (see claim 2). The NGAL assay result is then compared to a cutoff level selected to identify a renal tubular cell injury (i.e., correlating the level of detected antibody-NGAL complex to the mammal having a renal tubular cell injury; see especially step b) of claim 31).

Copending application No. 11/096,113 further recites that the sample may be taken at defined time periods in relation to the receipt of a procedure or onset of a condition such as ischemic renal injury, coronary bypass surgery, cardiac surgery, kidney transplantation, etc. For example, the sample can be obtained within 6 hours, 4 hours, 2 hours, and 30 minutes (see (see claims 22-23, 27-28, and 35-37).

The claims of the copending application differ from the instantly claimed invention in that in application No. 11/096,113 the sample assayed for NGAL is *blood or serum* (see claims 2, 9, and 24 in particular), while the sample assayed in the instant invention is *urine.*

However, it was well known to one skilled in the art of biochemical assay at the time of the invention that urine is a non-invasive and easily collected type of sample. See for example

Ramsden et al., column 1, lines 15-16, which teaches that urine samples are noninvasive and convenient. In addition, it was known in the prior art that NGAL is excreted in urine: Blaser et al. teach detection of human neutrophil lipocalin (NGAL) in urine by sandwich ELISA (see in particular the abstract; page 139, section 2.4; and pages 142-143, sections 3.3-3.4). Moses et al. also teach that NGAL may be detected in human urine by Western Blot (Example 2 and Figure 1B).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to detect NGAL in urine rather than in blood or serum for the advantages of ease of collection associated with the non-invasive nature of urine sampling, as taught by Ramsden et al. In light of the teachings of Blaser et al. and Moses et al., one skilled in the art would have a reasonable expectation of success in using urine as a sample source for detection of NGAL in response to renal injury since NGAL was also known to be excreted in urine.

This is a provisional obviousness-type double patenting rejection.

23. Claims 2, 4-5, 9-11, 33, 35, 37, 55, and 66 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 30-31, 33-45, and 47-50 of copending Application No. 11/770,422 in view of David et al., either one of Matthaeus 1 or 2, and either one of Sanicola-Nadel et al. or Muramatsu et al.

Copending Application No. 11/770,422 recites a method of diagnosing renal disorder by providing a sample of body fluid from a subject (which may be urine) and detecting the concentration of NGAL in the sample (see especially claims 30 and 45). The renal disorder may

be an acute renal tubular cell injury such as acute renal failure, acute tubular necrosis, or acute tubulo-interstitial nephropathy (i.e., renal tubular cell injuries; see claim 40).

The copending application differs from the instant claims in that although it recites that NGAL can be measured by means of a specific binding molecule, it does not specify antigen-antibody binding. In addition, the copending application fails to specifically recite that the renal disorder is an *ischemic* injury, or that NGAL is detected in *urine* samples obtained *within four hours* of the ischemic renal tubular cell injury.

Immunoassays involving antibodies, including those involving a primary "capture" antibody and secondary labeled antibody in a "sandwich" immunoassay format, were well known in the art to be sensitive and rapid means of detecting analytes in samples.

For example, David et al. teach sandwich or "two-site" immunoassays for detecting the presence of analytes in fluids, in which an unlabeled "capture" antibody is bound to a media (solid support) and then contacted with a sample containing the analyte (see in particular the abstract; column 3, line 10 to column 6, line 61, and especially column 4, lines 19-37). After formation of a capture antibody-analyte complex, a second labeled antibody is added which recognizes a different site on the analyte, resulting in the formation of a "sandwich" (see especially column 1, line 47 to column 2, lines 17; column 5, lines 45-60). This type of assay format has great utility in detecting the presence or amount of an analyte, and the improvements reported by David et al. also produce an assay format that is rapid and sensitive while eliminating false positive results (column 8, lines 33-38; and also column 1, line 67 to column 2, line 7).

Therefore, it would have obvious to one of ordinary skill in the art to detect NGAL in the methods of the copending application by the well known two-antibody sandwich immunoassay format, e.g. as taught by David et al. One would be motivated to employ this method to detect the presence of NGAL because it is well recognized in the prior art to be a rapid and sensitive method of detecting analytes in a fluid sample.

Further, based on the teachings of Matthaeus 1 and 2 which establish that NGAL is upregulated in the context of *ischemic* renal injury, it would have been obvious to diagnose renal disorders that are ischemic injuries according to the methods of the '422 application.

With respect to the limitation that the urine sample is obtained within four hours of the injury, Muramatsu (discussed above) exemplifies the renal ischemic injury biomarker Cyr61 at time points of 3-6, 6-9, 9-12, 12-18, and 18-24 hours after ischemia (see especially the legend to Figure 8) and report that the levels of urinary Cyr61 were seen to increase within 3-6 hours (page 1608). When taken together with the general knowledge in the art regarding the urgency of detecting disease as early as possible, it would also have been obvious to detect urinary NGAL as a biomarker of renal disorder as early as possible in this same manner.

Similarly, Sanicola-Nadel et al. (discussed above) teaches that proteins that are selectively upregulated following injury to a kidney can be identified at any time within one week following any insult that results in injury to renal tissue. It is noted that the claimed range of a sample obtained "within four hours of the RTCI" lies inside the prior art range of detection "within one week" disclosed by Sanicola-Nadel et al.

When taken together with the teachings of Matthaeus 1 or Matthaeus 2, , therefore, it would have been *prima facie* obvious to arrive at the claimed range of "within four hours" by

selecting any time period within the prior art range of "within one week" as taught by Sanicola-Nadel et al. See MPEP 2144.05 (I) when performing the methods of the copending application. Furthermore, when taken together with the general knowledge in the art regarding the urgency of detecting disease as early as possible, it would also have been obvious to detect urinary NGAL as a biomarker of renal disorder as early as possible in this same manner.

24. Claims 2, 4-5, 9-11, 33, 35, 37, 55, and 66 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 22, 24-36, 38-42 and 44 of copending Application No. 11/770,372 in view of David et al., Ramsden et al., Blaser et al., Moses et al., either one of Matthaeus 1 or 2, and either one of Sanicola-Nadel et al. or Muramatsu et al. See the analysis that follows.

25. Claims 2, 4-5, 9-11, 33, 35, 37, 55, and 66 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 29, 31-43, and 45-49 of copending Application No. 11/770,245 in view of David et al., Ramsden et al., Blaser et al., Moses et al., either one of Matthaeus 1 or 2, and either one of Sanicola-Nadel et al. or Muramatsu et al.

Copending application No. 11/770,372 recites a method of diagnosing renal disorder in humans by determining the concentration of NGAL in a body fluid sample (see especially claim 29). The renal disorder may be an acute renal tubular cell injury such as acute renal failure, acute tubular necrosis or acute tubulo-interstitial nephropathy (claim 39) and may be caused by a nephrotoxic agent (see claim 40).

Similarly, Copending application No. 11/770,245 recites a method of diagnosing renal disorder in humans by determining the concentration of NGAL in a body fluid sample (see especially claim 29). The renal disorder may be an acute renal tubular cell injury such as acute renal failure, acute tubular necrosis or acute tubulo-interstitial nephropathy (claim 39) and may be caused by a nephrotoxic agent (see claim 40).

The copending applications, like those discussed immediately above, differ from the instant claims in that although it recites that NGAL can be measured by means of a specific binding molecule, they does not specify antigen-antibody binding. In addition, the copending applications fail to specifically recite that the renal disorder is an ischemic injury, or that NGAL is detected in urine samples obtained within four hours of the ischemic renal tubular cell injury.

However, these features are found obvious in view of the teachings of Matthaeus 1 or 2 and either Sanicola-Nadel et al. or Muramatsu et al., for reasons discussed in detail above.

The copending applications also differ from the instant claims in that although the references specify a body fluid sample, urine is not specifically recited.

However, in light of the teachings of Ramsden et al., Blaser et al. and Moses et al. discussed in detail above, it would have been obvious to one of ordinary skill in the art at the time of the invention to detect NGAL in urine rather than in blood or serum (as recited in the copending applications) with a reasonable expectation of success.

26. Claim 60 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 30-31, 33-45, and 47-50 of copending Application No. 11/770,422 in view of David et al., Matthaeus 1, and either one of Sanicola-Nadel et al. or

Muramatsu et al. as applied to claim 66 above, and further in view of Zanardo et al. See the analysis that follows.

27. Claim 60 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 22, 24-36, 38-42 and 44 of copending Application No. 11/770,372 in view of David et al., Ramsden et al., Blaser et al., Moses et al., either one of Matthaeus 1 or 2, and either one of Sanicola-Nadel et al. or Muramatsu et al. as applied to claim 66 above, and further in view of Zanardo et al. See the analysis that follows.

28. Claim 60 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 29, 31-43, and 45-49 of copending Application No. 11/770,245 in view of David et al., Ramsden et al., Blaser et al., Moses et al., either one of Matthaeus 1 or 2, and either one of Sanicola-Nadel et al. or Muramatsu et al. as applied to claim 66 above, and further in view of Zanardo et al.

Copending Application Nos. 11/770,422, 11/770,372, and 11/770,245 are as discussed above, which further fail to specifically recite that the method is performed on a patient who has undergone open heart surgery.

However, based on the teachings of Zanardo et al. discussed in detail above that patients who undergo open heart surgery are at risk for developing acute renal failure, it would have been obvious to one of ordinary skill in the art to select such patients when performing the prior art methods of detecting acute ischemic renal failure as discussed in detail above. One would be motivated to do this because such patients were known to be at risk of acute renal failure. As such, when taken together with the general knowledge in the art, it would have been obvious to

combine the reference teachings in this manner so as to screen those individuals at risk for the presence of disease.

With respect to the recitation that the sample is obtained at 2 hours, which is presumed to refer to 2 hours after open heart surgery (see rejection under § 112, 2nd paragraph above), Zanardo et al. measured serum creatinine as a marker of renal function at the time of weaning from CBP (see Table II). As listed in the Table, bypass time was approximately 2-3 hours (see "CBP time (min)").

It would have been obvious to detect NGAL in patients undergoing CBP at the time of CPB weaning in this same manner, in order to assess renal function. Because bypass time is disclosed by Zanardo et al. to last approximately 2-3 hours, it would have been obvious to arrive at the claimed invention depending on the particular bypass time for the patient under study.

With respect to the recitation that the level of antibody-NGAL complex in the sample correlates with the RTCI progressing to ARF, Matthaeus 1 teaches that NGAL is upregulated in the context of acute renal failure induced by ischemic injury (see entire selection, including title). Consequently, when detecting NGAL as an indicator of renal function in CBP patients according to the prior art methods as discussed above, it would be to be expected and would also necessarily follow that antibody-NGAL complex levels would correlate with the progression to ARF in these patients.

Response to Arguments

29. Applicant's arguments filed 3/4/2009 have been fully considered.

30. With respect to the rejections under § 103 over either Matthaeus 1 or 2 in view of Ramsden, Blaser, Moses, and Muramatsu (or alternatively over either Matthaeus 1 or 2 and Ohlsson in view of Ramsden, Blaser, Moses, and Muramatsu), Applicant's arguments (Reply, pages 9-14) have been fully considered. Applicant has also submitted a Supplemental Declaration under 37 CFR 1.131 by inventors Prasad Devarajan and Jonathan Barasch in order to demonstrate conception and reduction to practice of the claimed invention in the United States prior to the effective date of the Muramatsu reference.

The Supplemental Declaration filed on 3/4/09 under 37 CFR 1.131 has been considered but is ineffective to overcome the rejections under §103(a) based on the Muramatsu et al. and/or Ohlsson et al. references, for the following reasons.

With respect to instant **claims 37 and 60**, it is noted that these claims have an effective filing date of 3/29/2004 (see *Priority* above). Therefore, the Supplemental Declaration is ineffective to overcome the rejections of these claims because the Muramatsu et al. reference, with a publication date of November, 2002, constitutes prior art under 102(b) and thus is not subject to be antedated under 37 CFR 1.131.

With respect to instant **claims 1, 4-5, 9-11, 33, 35, 55, and 66**, it is noted that the claims are directed to a method of detecting a renal tubular cell injury (see new claim 66).

The Supplemental Declaration states that experiments were performed prior to November 1, 2002 in which NGAL was detected in the urine in mice in whom an acute ischemic-reperfusion injury was induced by clamping of the kidney arteries (see especially at page 3, item 7). Applicants state that these experiments show conception and reduction to practice of a

method for the detection of a renal tubular cell injury in mammals (see especially at pages 3-4, item 11).

However, the experiments are not commensurate with the scope of the claims. In particular, the claims require "detection of a renal tubular cell injury", which conveys determination that an injury is present, i.e. diagnosis. By contrast, in the experiments reported in the Supplemental Declaration, the injury was surgically induced by the researchers and therefore known to be present beforehand. While the experiments also involved detection of NGAL in urine samples, the evidence presented does not indicate that ischemic renal injury was *detected*.

For these reasons, while the evidence of the Supplemental Declaration has been considered, it is not found sufficient to demonstrate conception and reduction to practice of the claimed invention in the United States prior to the effective date of the Muramatsu reference. No statements regarding diligence have been advanced by Applicant.

Applicant does not separately argue the limitation of dependent claims 2, 4, 9-11, 55, or 60 (see Reply, pages 12-14).

31. With respect to the provisional obviousness-type double patenting rejections over copending Application No. 11/096,113 and 11/770,372, Applicant argues that the copending applications requires a blood sample, while the instant claims require a urine sample (Reply, pages 15-17). Applicant argues that consequently, the claims of these copending applications cannot be the "same" as those of the instant application under MPEP 804, and argues that the circumstances described in *In re Schneller* are not applicable. Applicant further argues that neither application has yet issued as a patent. Applicant further argues that the present

application has a filing date that precedes the earliest priority date and filing date of the copending application.

This is not found persuasive because it does not necessarily follow that a nonstatutory double patenting rejection is inapplicable simply because the claims are not the "same", as made clear in the passage from MPEP 804 to which Applicant points. Therefore, arguments that the claims are not the "same" are not persuasive because this is not the standard for nonstatutory obviousness-type double patenting; conflicting claims to different inventions that are not patentably distinct are subject to rejections on the grounds of nonstatutory obviousness-type double patenting. See also MPEP 801, chart I-B.

Applicant's arguments that the circumstances described *In re Schneller* are not applicable are not on point because the double patenting rejections of record are not of the atypical *In re Schneller* type.

With respect to the argument that neither application has yet issued as a patent, and that the present application has an earlier filing date, Applicant is referred to MPEP 804 (I) B:

> [T]he courts have sanctioned the practice of making applicant aware of the potential double patenting problem if one of the applications became a patent by permitting the examiner to make a "provisional" rejection on the ground of double patenting. In re Mott, 539 F.2d 1291, 190 USPQ 536 (CCPA 1976); In re Wetterau,356 F.2d 556, 148 USPQ 499 (CCPA 1966). The merits of such a provisional rejection can be addressed by both the applicant and the examiner without waiting for the first patent to issue.
>
> If a "provisional" statutory double patenting rejection is the only rejection remaining in both applications, the examiner should withdraw that rejection in the application with the earlier filing date and permit that application to issue as a patent.

Applicant's arguments are not persuasive because in the instant case, the provisional double patenting rejections are not the only remaining rejection, and are therefore maintained at this time for reasons of record.

Finally, with respect to Application No. 11/770,372, the Examiner notes that the copending application is not limited to blood but rather recites a "sample of body fluid", which would encompass urine as claimed instantly.

32. Applicant acknowledges but does not presently address the provisional non-statutory obviousness-type double patenting rejections over copending Application Nos. 11/770,422 or 11/770,245 (see Reply, pages 17-18), which are therefore maintained at this time for reasons of record.

Conclusion

33. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Foster whose telephone number is (571) 272-8786. The examiner can normally be reached on M-F 6:30-3:00. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark Shibuya, can be reached at (571) 272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Christine Foster/
Examiner, Art Unit 1641

/Christopher L. Chin/
Primary Examiner, Art Unit 1641